

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
7 February 2002 (07.02.2002)

PCT

(10) International Publication Number
WO 02/09666 A1

- (51) International Patent Classification⁷: **A61K 9/00**
- (21) International Application Number: **PCT/EP01/08688**
- (22) International Filing Date: **27 July 2001 (27.07.2001)**
- (25) Filing Language: **English**
- (26) Publication Language: **English**
- (30) Priority Data:
0018322.8 27 July 2000 (27.07.2000) GB
- (71) Applicant (for all designated States except US): **THE BOOTS COMPANY PLC [GB/GB]; 1 Thane Road West, Nottingham, Nottinghamshire NG2 3AA (GB).**
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **KEATING, David, Anthony [GB/GB]; The Boots Company PLC, 1 Thane Road West, Nottingham, Nottinghamshire NG2 3AA (GB). NORMAN, Kurt [GB/GB]; The Boots Company PLC, 1 Thane Road West, Nottingham, Nottinghamshire NG2 3AA (GB).**
- (74) Agent: **JONES, Stephen, Anthony; AdamsonJones, Broadway Business Centre, 32a Stoney Street, Nottingham, Nottinghamshire NG1 1JJ. (GB).**
- (81) Designated States (national): **AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.**
- (84) Designated States (regional): **ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).**
- Published:**
- with international search report
 - before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

WO 02/09666 A1

(54) Title: **PHARMACEUTICAL EXTEMPORARY COMPOSITIONS**

(57) Abstract: A liquid pharmaceutical composition is prepared by mixing, prior to administration to a patient in need thereof, a first part comprising a flavoured or unflavoured liquid carrier and one or more second parts comprising a solid or liquid unit dose of the medicament to be administered.

PHARMACEUTICAL EXTEMPORARY COMPOSITIONS

The present invention relates to pharmaceutical compositions.

5 In order to make medicines palatable and to make it easier for patients, for example the aged, infirm or children, who have difficulty in swallowing the usual solid dosage forms to take their medicine, it has been common practice for formulate medicines as a thickened or gelled liquid. This type of medicine is not, however, totally satisfactory for several reasons. These include:

10

1. great care must be taken to ensure that the formulations are stable and that there is no reduction in potency on storage;

15

2. the flavouring system will be one chosen by the manufacturer of the formulation and it may not be acceptable to all patients. Indeed some patients may be so deterred by the flavour chosen by the manufacturer that they will refuse to take their medicines at all;

20

3. active ingredients found in formulations can make the preparation taste unpleasant and bitter;

25

4. if the illness being treated is short in duration, then the patient may not need all the pharmaceutical composition in the container. The remainder will then either be discarded which is wasteful or will be stored, often in less-than-ideal conditions until the same illness recurs. By that time the formulation may have degraded so that it is less effective in treating the illness.

30

5. combination products can be difficult and lengthy to develop, in some combination products global acceptability is often not applicable; and

6. pharmacists find it difficult to prescribe combination products.

The present invention provides a liquid pharmaceutical composition prepared by mixing immediately prior to administration to a patient in need thereof a first part which comprises a flavoured or unflavoured liquid carrier and one or more second parts comprising a solid or liquid unit dose of the medicament to be administered. The medicament is contained as either a single unit dose or as several unit doses which can be dispensed separately.

It is envisaged that a range of liquid carriers will be available having different flavours or no flavour. It will therefore be possible to choose the flavour which is most acceptable to the patient. By choosing an acceptable tasting carrier, the patient will be more likely to take the medicine and so much better patient compliance can be anticipated. The liquid carrier may contain water and glycerol or sorbitol to provide a satisfactory mouthfeel. The amount of glycerol or sorbitol may be from 5 to 20%, preferably 8 to 15% by volume of the liquid carrier. A natural or synthetic sweetener may be included. Natural sweeteners include glucose, sucrose or maltitol. Artificial sweeteners include saccharin and pharmaceutically acceptable salts thereof, acesulphame or aspartame. The flavouring may be any of the commercially available flavourings which would be acceptable to the patient. An organic acid, for example citric acid, may be present as a flavour enhancer. The liquid carrier may be thickened with any of the known pharmaceutically acceptable thickening agents. Suitable thickening agents include starch, sodium carboxymethyl cellulose, hydroxypropyl methyl cellulose, microcrystalline cellulose, gums (such as tragacanth, acacia, carrageenan and xanthan gums), pectin, gelatin, polyethyleneglycol and partially neutralised carbomers. Preservatives, such as sodium benzoate, parabens or bronopol may be included to ensure that the liquid carrier has an acceptable shelf life. As the liquid carrier does not contain any medicaments the time consuming and expensive stability trials, which are usually needed during the development of a pharmaceutical composition to ensure that there are no undesirable interactions between any particular medicament and the carrier, are not required.

The liquid carrier may be contained in any suitable container made, for example, of glass or synthetic polymeric material. Because the contents of the container do not contain any active medicament, there is no necessity to have a so-called "child-resistant" closure on the container. These closures, which are intended to make it difficult for children to open and consume medicines accidentally, can be difficult for the aged and infirm to open. The fact that they are not needed is therefore of significant benefit to this class of patient.

The one or more second parts of the formulation may be a unit dose of the pure medicament in solid form or liquid form. This may be combined with other pharmaceutical acceptable ingredients. Alternatively a multiple dose of the medicament in a solid or liquid form, this may be pure or combined with other pharmaceutical acceptable ingredients. The other pharmaceutically acceptable ingredients may comprise 0.1% to 99.9% of the unit dose. Suitable other ingredients include taste masking agents, diluents, binders, lubricants, sweeteners and flavours.

The active medicament may be an analgesic or anti-inflammatory, decongestant, cough suppressant, expectorant, antihistamine, antiallergy agent, agent for treating the gastrointestinal tract (for example antacid, antireflux agent, antiulcer agent, antidiarrhoeal agent, laxative or antiemetic), agent to counter motion sickness, antiviral agents, antifungal agents, antibacterial agents, diuretic agents, antiasthmatic agents, antimigraine agents, vitamins and/or minerals.

Suitable analgesics include aspirin, paracetamol (acetaminophen) and non-steroidal anti-inflammatory/analgesics such as diclofenac, indomethacin, mefenamic acid, nabumetone, tolmetin, piroxicam, felbinac, diflunisal, ibuprofen, flurbiprofen, naproxen and ketoprofen or pharmaceutically acceptable salts thereof (for example the sodium or lysine salts) or narcotic analgesics such as codeine and pharmaceutically acceptable salts thereof (for example codeine, phosphate or sulphate). Caffeine may be present in analgesic products to enhance the analgesic effect.

The amount of aspirin in a unit dose may be in the range 75 to 800 mg, preferably 200-600 mg, most preferably 75, 150, 300, 400 or 600 mg. The amount of paracetamol in a unit dose may be 50 to 2000 mg, preferably 120 to 1000 mg, most preferably 120, 250, 500 or 1000 mg. The amount of diclofenac in a unit dose may be 10 to 100 mg, preferably 20 to 80 mg, most preferably 25 or 50 mg. The amount of indomethacin in a unit dose may be in the range 25-75 mg, preferably 25 mg, 50 mg or 75 mg. The amount of mefenamic acid in a unit dose may be in the range 250-500 mg, preferably 250 mg or 500 mg. The amount of nabitmetone in a unit dose may be in the range 500-1000 mg. The amount of piroxicam in a unit dose may be in the range 10-40 mg, preferably 10, 20 or 40 mg. The amount of diflunisal in a unit dose may be in the range 250-500 mg, preferably 250 mg or 500 mg. The amount of ibuprofen in a unit dose may be in the range 50 to 800 mg, preferably 100 to 400 mg, most preferably 100, 200 or 400 mg. The amount of flurbiprofen in a unit dose may be 25 to 200 mg, preferably 50 to 150 mg, most preferably 50 or 100 mg. The amount of naproxen in a unit dose may be 100 to 800 mg, preferably 200 to 600 mg, most preferably 250, 373 or 500 mg. The amount of ketoprofen in a unit dose may be 25 to 250 mg, preferably 50 to 150 mg, most preferably 50 or 100 mg. The amount of codeine in a unit dose may be 20 to 50 mg, preferably 5 to 30 mg, most preferably 8, 12.5, 16 or 25 mg. If pharmaceutically effective salts of the above compounds are used then the amount of salt should be increased to give a dose of the free medicament corresponding to the figures given above. The amount of caffeine in a unit dose may be 5 to 200 mg, preferably 10 to 100 mg, most preferably 30, 45, 60 or 100 mg.

Suitable decongestants include ephedrine, levomethol, pseudoephedrine preferably as its hydrochloride, phenylpropanolamine preferably as its hydrochloride and phenylephrine.

30

The amount of ephedrine in a unit dose may be in the range 15-60 mg. The amount of levomethol in a unit dose may be in the range 0.5-100 mg, preferably

0.5-25 mg, most preferably 1, 2, 5, 10 or 25 mg. The amount of pseudoephedrine preferably as its hydrochloride in a unit dose may be in the range 60-120 mg, preferably 30, 60 or 120 mg. The amount of phenylpropanolamine preferably as its hydrochloride in a unit dose may be in the range 5-50 mg, preferably 5-20 mg.

- 5 The amount of phenylephrine in a unit dose may be in the range 5-25 mg, preferably 5, 10 or 25 mg.

Suitable cough suppressants include bibenzonium preferably as its bromide, caramiphen, carbetapentane preferably as its citrate, codeine, dextromethorphan
10 preferably as its hydrobromide, noscapine and pholcodeine.

The amount of bibenzonium bromide in a unit dose may be in the range 20-30 mg. The amount of caramiphen in a unit dose may be in the range 5-20 mg, preferably 5 or 20 mg. The amount of carbetapentane citrate in a unit dose may be in the
15 range 15-30 mg. The amount of codeine in a unit dose maybe in the range 2-50 mg, preferably 5-30mg, most preferably 10 mg. In the present invention pharmaceutically acceptable salts of codeine may also be used (for example codeine phosphate or sulphate). The amount of dextromethorphan hydrobromide in a unit dose may be in the range 15-30 mg, preferably 15 or 30 mg. The amount
20 of noscapine in a unit dose may be in the range 15-30 mg. The amount of pholcodeine in a unit dose may be in the range 2-25 mg, preferably 5 to 20 mg, more preferably 10 to 15 mg.

Suitable expectorants include ammonium bicarbonate, ammonium chloride,
25 bromhexine hydrochloride, cocillana creosote, guaifenesin, ipecacuanha, potassium and pharmaceutically acceptable salts thereof (for example potassium citrate or iodide), potassium guaicol sulfonate, squill and terpin hydrate.

The amount of ammonium bicarbonate in a unit dose may be in the range 300-600
30 mg. The amount of ammonium chloride in a unit dose may be in the range 0.3-2 g (300-2000 mg). The amount of bromhexine hydrochloride in a unit dose may be in the range 24-64 mg. The amount of creosote in a unit dose may be in the range

- 0.12-0.6 ml. The amount of guaifenesin in a unit dose may be in the range 100-200 mg, preferably 100 mg. The amount of ipecacuanha in a unit dose may be in the range 25-100 mg. The amount of potassium iodide in a unit dose may be in the range 150-300 mg, preferably 100 mg. The amount of potassium citrate in a unit dose may be in the range 150-300 mg, preferably 100 mg. The amount of potassium guericolsulfonate in a unit dose may be 80 mg. The amount of squill in a unit dose may be in the range 60-200 mg. The amount of terpin hydrate in a unit dose may be in the range 125-600 mg, preferably 300 mg.
- 10 Suitable antihistamines include azatadine or a salt thereof such as the maleate, bromodiphenhydramine or a salt thereof such as the hydrochloride, brompheniramine or a salt thereof such as the maleate, carbinoxamine or a salt thereof such as the maleate, chlorpheniramine or a salt thereof such as the maleate, cyproheptadine or a salt thereof such as the hydrochloride, 15 dextbrompheniramine or a salt thereof such as the maleate, dexchlorpheniramine or a salt thereof such as the maleate, diphenhydramine or a salt thereof such as the hydrochloride, doxylamine or a salt thereof such as the succinate, phenidamine or a salt thereof such as the tartrate, promethazine or a salt thereof such as the hydrochloride, pyrilamine or a salt thereof such as the maleate, pyrilamine or a salt thereof such as the tannate, tripeleminamine or a salt thereof such as the hydrochloride, tripolidine or a salt thereof such as the hydrochloride, cetirizine or a salt thereof such as the hydrochloride, cinnarizine, mequitazine, dcivastine.
- 20 The amount of azatadine in the form of maleate in a unit dose may be in the range 1-2 mg, preferably 1 mg. The amount of bromodiphenhydramine in the form of hydrochloride in a unit dose may be 3.75 mg. The amount of brompheniramine in the form of maleate in a unit dose may be in the range 4-12 mg, preferably 4, 8 or 12 mg. The amount of carbinoxamine in the form of maleate in a unit dose may be 4 mg. The amount of chlorpheniramine in the form of maleate in a unit dose may be in the range 2-12 mg, preferably 4, 8 or 12 mg. The amount of dextbrompheniramine in the form of maleate in a unit dose may be 6 mg. The amount of dexchlorpheniramine in the form of maleate in a unit dose may be in the
- 25 30

- range of 2-6 mg, preferably 2, 4 or 6 mg. The amount of diphenhydramine in the form of hydrochloride in a unit dose may be in the range of 12.5 to 200 mg, preferably 12.5-50 mg, more preferably 12.5, 25 or 50 mg. The amount of doxylamine in the form of succinate in a unit dose may be in the range 7.5-10 mg, preferably 7.5 or 10 mg. The amount of phenidamine in the form of tartrate in a unit dose may be in the range 5-10 mg, preferably 5 or 10 mg. The amount of promethazine in the form of hydrochloride in a unit dose may be in the range 1.5-6 mg. The amount of pyrilamine in the form of maleate in a unit dose may be 12.5 mg. The amount of pyrilamine in the form of tannate in a unit dose may be 12.5 mg. The amount of tripeleminamine in the form of hydrochloride in a unit dose may be in the range 25-50 mg, preferably 25, 37.5 or 50 mg. The amount of triprolidine in the form of hydrochloride in a unit dose may be in the range 1-2.5 mg, preferably 1.25-2.5 mg, most preferably 1.25 mg. The amount of cetirizine in a unit dose may be in the range 5-10 mg, preferably 5 mg or 10 mg. The amount of cinnarizine in a unit dose may be in the range of 15-75 mg, preferably 15 mg or 75 mg. The amount of mequitazine in a unit dose may be in the range 5-10 mg, preferably 5 mg or 10 mg. The amount of acrivastine in a unit dose may be 3-20 mg, preferably 5-10 mg, most preferably around 8 mg.
- 20 Suitable antiallergy agents include astemizole, clemastine or a salt thereof such as the hydrogen fumarate, loratadine, terfenodine.

- The amount of astemizole in a unit dose may be in the range 0.5-200 mg, preferably 1-100 mg, most preferably 2, 5, 10, 20 or 40 mg. The amount of clemastine in the form of its hydrogen fumarate in a unit dose may be in the range 0.01-200 mg, preferably 0.1-10 mg, most preferably 0.2, 0.4, 0.6, 1.2 or 2.4 mg. The amount of loratadine in a unit dose may be in the range 0.5-200 mg, preferably 1-100 mg, most preferably 2, 5, 10, 20 or 40 mg. The amount of terfenadine in a unit dose may be in the range 5-1000 mg, preferably 10-600 mg, most preferably 20, 40, 60, 100 or 200 mg.

Suitable antacids include aluminium glycinate, aluminium hydroxide gel, aluminium phosphate gel, dried aluminium phosphate gel, calcium carbonate, charcoal, hydrotalcite, light kaolin, magnesium carbonate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, sodium bicarbonate.

5

The amount of aluminium glycinate in a unit dose may be in the range 0.1-10 g, preferably 0.1-5g, most preferably 0.2, 0.5, 1 or 2 g. The amount of aluminium hydroxide gel in a unit dose may be in the range 1-50 ml, preferably 2-30 ml, most preferably 5, 7.5, 10, 15 or 30 ml. The amount of aluminium phosphate gel in a unit dose may be in the range 0.5-100 ml, preferably 1-50 ml, most preferably 2, 5, 10, 15 or 30 ml. The amount of dried aluminium phosphate gel in a unit dose may be in the range 50-5000 mg, preferably 100-2000 mg, most preferably 200, 400, 800 or 1600 mg. The amount of calcium carbonate in a unit dose may be in the range 0.1-30 g, preferably 0.5-10 g, most preferably 0.5, 1, 2 or 5 g. The amount of charcoal in a unit dose may be in the range 1-200g, preferably 1-100 g, most preferably 2, 4, 8, 16 or 50 g. The amount of hydrotalcite in a unit dose may be in the range 0.1-10 g, preferably 0.2-5 g, most preferably 0.5, 1 or 2 g. The amount of light kaolin in a unit dose may be in the range 10 mg-100 g, preferably 100 mg-75 g, most preferably 1, 10, 15, 20, 50 or 75 g. The amount of magnesium carbonate in a unit dose may be in the range 50 mg-10 g, preferably 50 mg-5 g, most preferably 100, 200 or 500 mg. The amount of magnesium hydroxide in a unit dose may be in the range 100 mg-10 g, preferably 100 mg-5 g, most preferably 100, 250, 500 or 750 mg. The amount of magnesium oxide in a unit dose may be in the range 100 mg-10 g, preferably 100 mg-5 g, most preferably 100, 250, 500 or 750 mg. The amount of sodium bicarbonate in a unit dose may be in the range 0.1-50 g, preferably 0.5-25 g, most preferably 0.5, 1, 2, 5 or 10 g.

20

25

Suitable antireflux agents include simethicone and sodium alginate.

30

The amount of simethicone in a unit dose may be in the range 5-1000 mg, preferably 10-500 mg, most preferably 25, 40, 50, 60, 100 or 200 mg. The amount

of sodium alginate in a unit dose may be in the range 50 mg-10 g, preferably 75 mg-5 g, most preferably 100, 250, 500 or 1 g.

Suitable antiulcer agents include bismuth subsalicylate, H₂ receptor antagonists
5 such as cimetidine, famotidine, ranitidine and nizatidine and proton pump inhibitors such as omeprazole, pantoprazole and lansoprazole.

The amount of bismuth subsalicylate in a unit dose may be in the range 250-2000 mg, preferably 50-1500 mg, most preferably 75, 150, 300, 600 or 1000 mg. The
10 amount of cimetidine in a unit dose may be in the range 10 mg-5 g, preferably 50 mg-2 g, most preferably 100, 200 or 400 mg. The amount of famotidine in a unit dose may be in the range 10-80 mg, preferably 20 or 40 mg. The amount of ranitidine in a unit dose may be in the range 100-600 mg, preferably 300-600 mg, most preferably 300 or 600 mg. The amount of nizatidine in a unit dose may be 50
15 to 500 mg, preferably 100 to 400 mg, more preferably 150 to 300 mg. The amount of omeprazole in a unit dose may be 5 to 50 mg, preferably 10 to 40 mg, more preferably 10, 20 or 40 mg. The amount of pantoprazole in a unit dose may be 10 to 50 mg, preferably 15 to 45 mg, more preferably 20 to 40 mg. The amount of lansoprazole in a unit dose may be 5 to 50 mg, preferably 10 to 40 mg, more
20 preferably 15 or 30 mg.

Suitable antidiarrhoeal agents include loperamide or a salt thereof, such as the hydrochloride, methylcellulose, diphenoxylate and morphine or a salt thereof, such
25 as the hydrochloride.

The amount of loperamide in the for of its hydrochloride in a unit dose may be in the range 0.1-50 mg, preferably 0.5-20 mg, most preferably 1, 2, 4 or 8 mg. The amount of methylcellulose in a unit dose may be in the range 20 mg-5 g, preferably 50 mg-4 g, most preferably 100, 200, 500 mg, 1 or 2 g. The amount of
30 diphenoxylate in the for of its hydrochloride in a unit dose may be 1-10 mg, preferably 2-5 mg, more preferably 2.5 mg. The amount of morphine in the for of

its hydrochloride in a unit dose may be in the range 20-4000 µg, preferably 50-2000µg, most preferably 100, 200, 400, 800 or 1600 µg.

Suitable laxatives include agar, aloin, bisacodyl, ispaghula husk, lactulose,
5 phenolphthalein and senna extract (including sennosides A + B).

The amount of agar in a unit dose may be in the range 1-200 mg, preferably 2-100 mg, most preferably 2-5, 5, 10, 20 or 50 mg. The amount of aloin in a unit dose may be in the range 1-200 mg, preferably 2-100 mg, most preferably 5, 10, 15 or
10 30 mg. The amount of bisacodyl in a unit dose may be in the range 0.1-100 mg, preferably 0.5-50 mg, most preferably 1, 2, 5, 10 or 20 mg. The amount of ispaghula husk in a unit dose may be in the range 100 mg-50 g, preferably 500 mg-25 g, most preferably 1, 2, 3, 5 or 10 g. The amount of lactulose in a unit dose may be in the range 100 mg-50 g, preferably 500 mg-30 g, most preferably 1, 2, 5,
15 10 or 15 g. The amount of phenolphthalein in a unit dose may be in the range 1-5000 mg, preferably 5-4000 mg, most preferably 7.5, 15, 30, 60, 100, 200 or 300 mg. The amount of senna extract (including sennosides A+B) in a unit dose may be in the range 0.5-100 mg, preferably 1-50 mg, most preferably 2.5, 5, 7.5, 10, 15 or 30 mg.

20

Suitable antiemetics include dimenhydrinate, metoclopramide or a salt thereof such as the hydrochloride, domperidone or a salt thereof such as the maleate, buclizine, cyclizine, prochlorperazine or a salt thereof such as the maleate, ipecacuanha, squill.

25

The amount of ipecacuanha in a unit dose may be in the range 25-100 mg. The amount of squill in a unit dose may be in the range 60-200 mg. The amount of domperidone may be in the range 5-50 mg, preferably 5, 10, 15, 20, 25, 30, 40 or 50 mg. The amount of buclizine in a unit dose may be in the range 2-100 mg, preferably 5-50 mg, more preferably 6.25, 13.5, 25, preferably 5-50 mg, more
30 preferably 6.25, 13.5, 25 or 50 mg. The amount of cyclizine in a unit dose may be in the range 1-50 mg, preferably 2-30 mg, more preferably 5, 7.5, 10, 15, 20 or 25

mg. The amount of metoclopramide in a unit dose may be in the range 2-30 mg, preferably 5, 10, 15 or 30 mg. The amount of dimenhydrinate in a unit dose may be in the range 5-50 mg, preferably 25 mg. The amount of prochlorperazine in a unit dose may be in the range 3-25 mg, preferably 3 mg or 5 mg. If
5 pharmaceutically effective salts of the above compounds are used then the amount of salt should be increased to give a dose of the free medicament corresponding to the figures given above.

Suitable agents to counter motion sickness include cinnarizine, dimenhydrinate,
10 hyoscine or a salt thereof such as the hydrobromide and meclozine or a salt thereof such as the hydrochloride.

The amount of cinnarizine in a unit dose may be in the range 0.5-200 mg, preferably 1-100 mg, most preferably 5, 10, 20, 40 or 60 mg. The amount of
15 dimenhydrinate in a unit dose may be in the range 1-500 mg, preferably 5-300 mg, most preferably 10, 20, 50, 100 or 250 mg. The amount of hyoscine hydrobromide in a unit dose may be in the range 0.01-1 mg, preferably 0.05-0.5 mg, most preferably 0.05, 0.1, 0.2, 0.3 or 0.5 mg. The amount of meclozine hydrochloride in a unit dose may be in the range 0.5-200 mg, preferably 1-100 mg, more preferably
20 2, 5, 10, 20 or 40 mg.

Suitable antiviral agents include aciclovir. The amount of aciclovir in a unit dose may be in the range 100 to 1000 mg, preferably 200 to 800 mg.

25 Suitable antifungal agents include fluconazole and terbinafine. The amount of fluconazole in a unit dose may be in the range 50-200 mg, preferably 50 mg or 200 mg. The amount of terbinafine may be in the range 250-500 mg, preferably 250 mg.

30 Suitable antibacterial agents include erythromycin and fusidic acid and salts thereof such as the sodium salt. The amount of erythromycin in a unit dose may

be in the range 125-500 mg, preferably 125 mg, 250 mg or 500 mg. The amount of fusidic acid in a unit dose may be in the range 250-500 mg, preferably 250 mg.

Suitable diuretics include frusemide. The amount of frusemide in a unit dose may
5 be in the range 20-80 mg, preferably 20, 40 or 80 mg.

Suitable anti-asthmatic agents include ketotifen. The amount of ketotifen in a unit dose may be in the range 1-4 mg, preferably 1 mg or 2 mg.

10 Suitable anti-migraine agents include sumatriptan. The amount of sumatriptan in a unit dose may be in the range 20-100 mg, preferably 20, 50 or 100 mg.

Suitable vitamins include A, B1, B2, B3, B5, B6, B12, C, D, E, folic acid, biotin, and K. Suitable minerals include calcium, phosphorus, iron, magnesium, zinc, iodine,
15 copper, chloride, chromium, manganese, molybdenum, nickel, potassium, selenium, boron, tin and vanadium.

The medicament may be taste masked to further improve the taste profile of the pharmaceutical composition. The medicament may be taste masked using
20 methods known in the art for example adding taste masking ingredients such as ethylcellulose, hydroxypropylmethylcellulose, methylethylcellulose, hydroxypropylcellulose, polyvinyl pyrrolidone, polyvinyl alcohol, mono glycerides, diglycerides, stearic acid, palmitic acid, gelatin, hydrogenated cotton seed oil and more generally any food grade polymer, starch, wax or fat. The taste masking agents
25 may be used singly or in combination.

Preferably the unit dose of medicament is granulated optionally with other excipients. The other excipients may include taste masking agents, sweeteners, flavours, diluents, binders, lubricants.

30

Suitable sweeteners include acesulfame K, sodium saccharin, aspartame, sucrose. The amount of sweetener may be in the range 0.001% to 0.1%.

Suitable flavours are available commercially and the flavour may be enhanced by the addition of an acid such as citric acid, ascorbic acid, tartaric acid.

- 5 Suitable diluents include calcium phosphate (anhydrous and dihydrate), calcium sulphate, carboxymethylcellulose calcium, cellulose acetate, dextrans, dextrin, dextrose, fructose, glyceryl palmitostearate, hydrogenated vegetable oil, kaolin, lactitol, lactose, magnesium carbonate, magnesium oxide, maltitol, maltodextrin, maltose, microcrystalline cellulose, polymethacrylates, powdered cellulose, 10 pregelatinised starch, silicified microcrystalline cellulose, sodium chloride, starch, sucrose, sugar, talc, xylitol. One or more diluents may be used. The amount of diluent may be in the range 10-98% w/w.

- Suitable binders include acacia, alginic acid, carboxymethylcellulose, cellulose, 15 dextrin, ethylcellulose, gelatin, glucose, guar gum, hydrogenated vegetable oil, hydroxyethylcellulose, hydroxypropylmethylcellulose, liquid glucose, magnesium aluminium silicate, maltodextrin, methylcellulose, polyethylene oxide, polymethacrylates, povidone, sodium alginate, starch, vegetable oil and zein. One or more binders may be used. The amount of binder may be in the range 10-50% 20 w/w.

- Suitable lubricants include calcium stearate, canola oil, glyceryl palmitostearate, hydrogenated vegetable oil, magnesium stearate, mineral oil, poloxamer, polyethylene glycol, polyvinyl alcohol, sodium benzoate, sodium lauryl sulphate, 25 sodium stearyl fumarate, stearic acid, talc and zinc stearate. One or more lubricants may be used. The lubricant may be in the range 0.01-10% w/w.

- The granules may be formed by methods known by the skilled man for example wet granulation or dry granulation.

30

The one or more second part of the pharmaceutical compositions of the present invention may be contained in a sealed container(s) prior to use. The sealed

container may be any suitable container such as a sachet, pouch, ampoule or capsule made from a material which is compatible with the medicament and any other ingredients which are present. The sealed container should be easy to open to enable all its contents to be poured from the container.

5

The first and one or more secondn parts of the pharmaceutical composition of the present invention are kept separate until just before use. When the patient requires a unit dose of the medicament to be administered the two parts of the pharmaceutical composition are mixed and swallowed by the patient. To mix the parts, a suitable quantity of the liquid carrier is poured into a mixing vessel. The exact quantity of liquid carrier is not critical but is envisaged that an amount between 10 and 50 ml, preferably 15 to 30 ml will be used. The mixing vessel may be provided with markings indicating the suggested quantities but this is not essential. The sealed container holding the unit dose of medicament is then opened and the contents are poured into the liquid carrier. The liquid carrier and the contents of the sealed container should then be mixed in any suitable manner for example by stirring or shaking. The preferred method of mixing is by shaking. To facilitate this the mixing vessel may be provided with a removable lid which when fitted to the mixing vessel seals the mixing vessel enabling the vessel to be shaken to distribute the unit dose of medicament throughout the liquid carrier. It is envisaged that the mixed contents of the mixing vessel will be ingested by the patient soon after mixing. Because of this there will be no time for any adverse interaction between the medicament and any of the excipients used in the liquid carrier as can sometimes occur in the prior art liquid compositions on storage.

20
25

A further aspect of the present invention also provides a kit of parts for preparing a liquid unit dosage form of a medicament comprising a container containing a flavoured liquid carrier, a sealed container containing a solid unit dose of the medicament to be dispensed and a mixing vessel in which the liquid carrier and unit dose of the medicament are mixed prior to ingestion by a patient in need thereof. Preferably the mixing vessel is provided with a lid which seals the container enabling the liquid carrier and the unit dose of medicament to be mixed

30

by shaking the sealed mixing vessel. The mixed pharmaceutical composition may then be ingested by the patient from the mixing vessel.

A yet further aspect of the present invention provides a method of preparing a liquid unit dosage form of a medicament which involves dispensing a quantity of a flavoured liquid carrier, opening a sealed container holding a solid unit dose of the medicament and mixing the unit dose of the medicament into said liquid carrier.

The pharmaceutical compositions of the present invention described herein have several advantages over the known liquid dosage forms.

1. Because the liquid carrier and the second or more part incorporating the medicament are mixed immediately prior to administration, there can be no interactions between the medicament and any of the excipients as sometimes occurs in the known compositions on storage because the medicament and excipients are in contact for long periods of time. Because of this possible instability of the known compositions, each one of them must be subjected to time consuming and expensive stability testing. In the present invention each flavoured variety of the liquid carrier must be tested but only once. There is no requirement to test the liquid carrier every time a composition containing a new medicament is required.
2. The medicaments are stored in separate containers in solid or liquid form. The possibility of interactions with other excipients in the known liquid compositions does not occur with the present invention. The contents of the container must, of course, undergo stability testing but this will be much simpler than testing the known liquid compositions.
3. The patient can choose the flavour of the liquid carrier for his or her medicine which is acceptable to him or her. This will improve patient compliance with the dosing regime.

4. The amount of wastage is reduced as the liquid carrier can be stored until it is needed again for use with a different medicament to treat different symptoms in the patient.
5. The present invention makes it easy to give combinations of medicaments which are specifically directed at the symptoms of any particular patient, by mixing the liquid carrier with unit doses of more than one medicament. In the known liquid compositions containing combinations of medicaments is selected by the manufacturer and it may not be the combination which is actually needed by any particular patient.
6. Taste will improve due to the bitterness of active ingredients being suppressed by tastemasking, therefore having a positive effect on the overall taste of the formulation.
7. The present invention avoids the present undesirable practice of storing a number of partly used liquid compositions which will be used again if the illness recurs. Using the present invention, any unconsumed liquid carrier can be used to treat a different illness by mixing into the liquid carrier a different solid unit dose of medicament.

The invention will be illustrated by the following Examples which are given by way of example only.

Example 1 – Sugar-free liquid carrier

<u>Ingredient</u>	<u>% weight or v/v</u>
Glycerol	10 v
Maltitol solution	30 v
Sodium benzoate	0.2 w
Citric acid	0.2 w

Acesulfame K	0.025 w
Sodium saccharin	0.0125 w
Liquid flavour	0.1 v
Purified water	to 100 v

5

The liquid carrier uses the sweetness and mouthfeel of glycerol and maltitol to give a good mouth-feel taste. Thickener systems may be used to give a thicker syrup.

Example 2 – Liquid carrier containing sugar

10

<u>Ingredient</u>	<u>% weight or v/v</u>
Glycerol	10 v
Liquid sugar demin	40 v
15 Sodium benzoate	0.2 w
Citric acid	0.2 w
Liquid flavour	0.1 v
Purified water	to 100 v

20 The base uses the sweetness and mouth-feel of glycerol and liquid sugar to give a good mouth-feel. Thickener systems may be used to give a thicker syrup.

Example 3

25

<u>Ingredient</u>	<u>mg/sachet</u>
Taste masked paracetamol	555.55
Total	555.55

30 Taste masked paracetamol is calculated as being 90% of paracetamol and 10% of ethyl cellulose as the taste masking ingredient. Therefore the actual dose of paracetamol is 500 mg.

The powdered taste masked medicament is sealed within a sachet. When the medicament is to be administered to the patient, the contents of the sachet are added to a quantity (preferably 5 to 30 ml) of the liquid carrier of either Example 1 or Example 2 and mixed by shaking. The resulting liquid dosage form is then taken by the patients.

Example 4

<u>Ingredient</u>	<u>mg/sachet</u>
Taste masked ibuprofen	285.71
Xylitol	274.29
Total	560

Taste masked ibuprofen is based on 70% of ibuprofen and 30% mono and diglycerides of fatty acids as the taste masking ingredient. Therefore the actual dose of ibuprofen is 200 mg.

The powdered taste masked medicament is sealed within a sachet. When the medicament is to be administered to the patient, the contents of the sachet are added to a quantity (preferably 5 to 30 ml) of the liquid carrier of either Example 1 or Example 2 and mixed by shaking. The resulting liquid dosage form is then taken by the patients.

Example 5

<u>Ingredient</u>	<u>mg/sachet</u>
Taste masked aspirin	375
Xylitol	190
Total	565

Taste masked aspirin is 80% aspirin, 20% ethyl cellulose as the taste masking agent. Therefore sachet contains 300 mg of the active ingredient.

5 The powdered taste masked medicament is sealed within a sachet. When the medicament is to be administered to the patient, the contents of the sachet are added to a quantity (preferably 5 to 30 ml) of the liquid carrier of either Example 1 or Example 2 and mixed by shaking. The resulting liquid dosage form is then taken by the patients.

10 **Example 6**

	<u>Ingredient</u>	<u>mg/sachet</u>
	Taste masked paracetamol	277.8
15	Lactose	222.2
	Total	500

Taste masked paracetamol is 90% paracetamol, 10% ethyl cellulose as the taste masking agent. Therefore a sachet contains 250 mg of the active ingredient.

20

The powdered taste masked medicament is sealed within a sachet. When the medicament is to be administered to the patient, the contents of the sachet are added to a quantity (preferably 5 to 30 ml) of the liquid carrier of either Example 1 or Example 2 and mixed by shaking. The resulting liquid dosage form is then
25 taken by the patients.

Example 7

30 The efficacy of the compositions of the present invention were demonstrated in the following way. The formulation of Example 6 was mixed with the sugar free liquid carrier of Example 1 and an expert panel were asked to compare the taste with that of a widely-used paediatric pain relief oral suspension containing paracetamol.

87% of the panel preferred the taste of the composition according to the present application.

CLAIMS

1. A liquid pharmaceutical composition prepared by mixing, prior to administration to a patient in need thereof, a first part comprising a flavoured or
5 unflavoured liquid carrier and one or more second parts comprising a solid or liquid unit dose of the medicament to be administered.
2. A pharmaceutical composition as claimed in claim 1 in which the liquid carrier comprises water, glycerol and/or sorbitol, and optionally a natural or
10 synthetic sweetener and/or thickening agent.
3. A pharmaceutical composition as claimed in claim 1 or claim 2 wherein the liquid carrier comprises a patient-acceptable flavouring and optionally an organic acid flavour enhancer.
15
4. A pharmaceutical composition as claimed in any preceding claims wherein unit dose of the medicament is stored in a sealed container prior to mixing.
5. A kit of parts for preparing a liquid unit dosage form of a medicament
20 comprising a container containing a flavoured liquid carrier, a sealed container containing a solid or liquid unit dose of the medicament to be dispensed and a mixing vessel in which the liquid carrier and unit dose of the medicament are mixed prior to ingestion by a patient in need thereof.
- 25 6. A kit as claimed in claim 5 in which the liquid carrier comprises water, glycerol and/or sorbitol, and optionally a natural or synthetic sweetener and/or thickening agent.
7. A kit as claimed in claim 5 or claim 6 wherein the liquid carrier comprises a patient-acceptable flavouring and optionally an organic acid flavour enhancer.
30
8. A kit as claimed in any one of claims 5 to 7 wherein unit dose of the medicament is stored in a sealed container prior to mixing.

9. A kit as claimed in any one of claims 5 to 8 wherein the mixing vessel is provided with a lid which seals the mixing vessel allowing the contents to be mixed by shaking the sealed mixing vessel.

5

10. A method of preparing a liquid unit dosage form of a medicament which involves dispensing a quantity of a flavoured liquid carrier, opening a sealed container holding a solid or liquid unit dose of the medicament and mixing the unit dose of the medicament into said liquid carrier.

10

11. A method as claimed in claim 10 in which the liquid carrier comprises water, glycerol and/or sorbitol, and optionally a natural or synthetic sweetener and/or thickening agent.

15 12. A method as claimed in claim 10 or claim 11 wherein the liquid carrier comprises a patient-acceptable flavouring and optionally an organic acid flavour enhancer.

20 13. A method as claimed in any one of claims 10 to 12 wherein unit dose of the medicament is stored in a sealed container prior to mixing.

25 14. A method as claimed in any one of claims 10 to 13 in which the mixing takes place in mixing vessel wherein the mixing vessel is provided with a lid which seals the mixing vessel allowing the contents to be mixed by shaking the sealed mixing vessel.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/08688

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 247 980 A (A. MENARINI) 2 December 1987 (1987-12-02) claims 1,4; example 1 ---	1-13
X	EP 0 597 414 A (ASTA MEDICA) 18 May 1994 (1994-05-18) claims 1-4 example 1 ---	1,3-5, 7-10, 12-14
X	EP 0 552 105 A (DESLANDES, REMY) 21 July 1993 (1993-07-21) claims 1,5 column 1, line 47 - line 52 column 2, line 21 - line 29 -----	1,4,5,8, 9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

19 December 2001

Date of mailing of the International search report

03/01/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Ventura Amat, A

INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No
PCT/EP 01/08688

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 247980	A	02-12-1987	IT 1204069 B	01-03-1989
			AT 66150 T	15-08-1991
			BE 905672 A1	16-02-1987
			DE 3772107 D1	19-09-1991
			EP 0247980 A2	02-12-1987
			ES 2039261 T3	16-09-1993
			GR 3003054 T3	17-02-1993
EP 597414	A	18-05-1994	GB 2272374 A	18-05-1994
			AT 189603 T	15-02-2000
			DE 69327829 D1	16-03-2000
			DE 69327829 T2	29-06-2000
			DK 597414 T3	29-05-2000
			EP 0597414 A2	18-05-1994
			ES 2142328 T3	16-04-2000
			GR 3033065 T3	31-08-2000
			PT 597414 T	30-06-2000
			US 5389372 A	14-02-1995
EP 552105	A	21-07-1993	FR 2686064 A1	16-07-1993
			DE 69301152 D1	15-02-1996
			DE 69301152 T2	05-09-1996
			EP 0552105 A1	21-07-1993